What is claimed is:

1. A peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of prostate specific antigen, wherein the peptide is 20 or fewer amino acids in length.

2. The peptide of claim 1, wherein the sequence comprises: the amino acids

$X_5X_4X_3X_2X_1$,

wherein X_5 is from 0 to 16 amino acids; X_4 is serine, isoleucine, or lysine; X_3 is serine or lysine; X_2 is leucine, tyrosine or lysine; and X_1 is glutamine, asparagine or tyrosine.

3. The peptide of claim 2, further comprising X_{-1} linked to X_1, wherein X_{-1} is from 1 to 10 amino acids.

4. The peptide of claim 2, wherein X_1 is glutamine.

5. The peptide of claim 2, further comprising amino acid X_6 linked to the amino terminus of X_5, wherein X_6 is from 0 to 15 amino acids and wherein X_5 is serine or lysine.

6. The peptide of claim 5, further comprising amino acid X_7 linked to the amino terminus of X_6, wherein X_7 is from 0 to 14 amino acids and wherein X_6 is histidine or asparagine.

7. The peptide of claim 3, wherein X_{-1} comprises leucine.

8. The peptide of claim 6, wherein the amino acid sequence is selected from the group consisting of His-Ser-Ser-Lys-Leu-Gln, Glu-His-Ser-Ser-Lys-Leu-Gln, Gln-Asn-Lys-Ile-Ser-Tyr-Gln, and Glu-Asn-Lys-Ile-Ser-Tyr-Gln.

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9. The peptide of claim 1, further comprising a capping group attached to the N-terminus of the peptide, the group inhibiting endopeptidase activity on the peptide.

9 8

10. The peptide of claim 9, wherein the capping group is selected from the group consisting of acetyl, morpholinocarbonyl, benzyloxycarbonyl, glutaryl and succinyl substituents.

10

11. The peptide of claim 1, wherein the cleavage of the peptide by the enzyme yields at least 5 picomoles of cleaved peptide per minute per 200 picomoles of enzyme.

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12. The peptide of claim 1, wherein the cleavage of the peptide in human serum yields at most 2.0 picomoles of cleaved peptide per minute.

12

13. A peptide of claim 1, further comprising an added substituent which renders the peptide water-soluble.

13 12

14. A peptide of claim 13, wherein the added substituent is a polysaccharide.

14 13

15. A peptide of claim 14, wherein the polysaccharide is selected from the group consisting of modified or unmodified dextran, cyclodextrin, and starch.

15 1

16. A peptide of claim 2, further comprising an antibody attached to the amino terminus of X_5, or X_4 when X_5 is 0.

17. A peptide composition comprising a plurality of peptides, each peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of prostate specific antigen, wherein each peptide has 20 or fewer amino acids.

18. A polynucleotide encoding the peptide of claim 1.

19. A composition comprising a prodrug, the prodrug comprising

a therapeutically active drug; and

a peptide of claim 1,

wherein the peptide is linked to the therapeutically active drug to inhibit the therapeutic activity of the drug, and wherein the therapeutically active drug is cleaved from the peptide upon proteolysis by an enzyme having a proteolytic activity of prostate specific antigen (PSA).

20. The composition of claim 19, wherein the peptide is linked directly to the therapeutic drug.

21. The composition of claim 20, wherein the peptide is linked directly to a primary amine group on the drug.

22. The composition of claim 19, wherein the peptide is linked to the therapeutic drug via a linker.

23. The composition of claim 22, wherein the linker is an amino acid sequence.

24. The composition of claim 23, wherein the linker comprises a leucine residue.

25. The composition of claim 19, wherein the therapeutically active drug inhibits a SERCA pump.

26. The composition of claim 25, wherein the therapeutically active drug is selected from the group of primary amine containing thapsigargins or thapsigargin derivatives.

27. The composition of claim 19, wherein the therapeutically active drug intercalates into a polynucleotide.

28. The composition of claim 27, wherein the therapeutically active drug is an anthracycline antibiotic.

29. The composition of claim 28, wherein the therapeutically active drug is selected from the group consisting of doxorubicin, daunorubicin, epirubicin and idarubicin.

30. The composition of claim 19, wherein the peptide is His-Ser-Ser-Lys-Leu-Gln-Leu.

31. The composition of claim 19, wherein the therapeutic drug is a compound belonging to the group of thapsigargins which have been derivatized with a moiety containing a primary amine group, the peptide is His-Ser-Ser-Lys-Leu-Gln, and the linker is selected from the group consisting of unsubstituted or alkyl-, aryl-, halo-, alkoxy-, alkenyl-, amido- or amino-substituted $CO\text{-}(CH{=}CH)_{n1}\text{-}(CH_2)_{n2}\text{-}Ar\text{-}NH_2$, $CO\text{-}(CH_2)_{n2}\text{-}(CH{=}CH)_{n1}\text{-}Ar\text{-}NH_2$, $CO\text{-}(CH_2)_{n2}\text{-}(CH{=}CH)_{n1}\text{-}CO\text{-}NH\text{-}Ar\text{-}NH_2$ and $CO\text{-}(CH{=}CH)_{n1}\text{-}(CH_2)_{n2}\text{-}CO\text{-}NH\text{-}Ar\text{-}NH_2$ wherein n1 and n2 are from 0 to 5, Ar is any substituted or unsubstituted aryl group, and attachment of NH_2 to Ar is in a ortho, meta or para position with respect to the remainder of the linker.

32. The composition of claim 19, wherein the therapeutically active drug has an IC_{50} toward ER Ca^{2+}-ATPase of at most 500 nM.

33. The composition of claim 32, wherein the therapeutically active drug has an IC_{50} toward ER Ca^{2+}-ATPase of at most 50 nM.

34. The composition of claim 19, wherein the therapeutically active drug has an LC_{50} toward PSA-producing tissue of at most 20 μM.

35. The composition of claim 34, wherein the therapeutically active drug has an LC_{50} toward PSA-producing tissue of less than or equal to 2.0 μM.

36. The composition of claim 19, wherein cleavage of the peptide by the enzyme yields at least 5 picomoles of cleaved peptide per minute per 200 picomoles of enzyme.

37. The composition of claim 19, wherein cleavage of the peptide in human serum yields at most 2.0 picomoles of cleaved peptide per minute.

38. The composition of claim 19, further comprising an added substituent which renders the composition water soluble.

39. The composition of claim 38, wherein the added substituent is a polysaccharide.

40. The composition of claim 39, wherein the polysaccharide is selected from the group consisting of modified or unmodified dextran, cyclodextrin and starch.

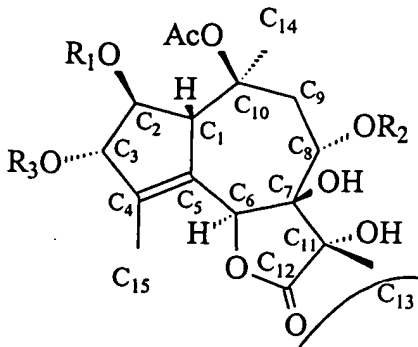
41. A therapeutically active sesquiterpene-γ-lactone derivative containing a primary amine.

42. The derivative of claim 41, wherein the sesquiterpene-γ-lactone is a thapsigargin derivative.

43. The thapsagargin derivative of claim 42, further comprising a boc protecting group.

44. The thapsigargin derivative of claim 42, wherein the derivative is linked to an antibody.

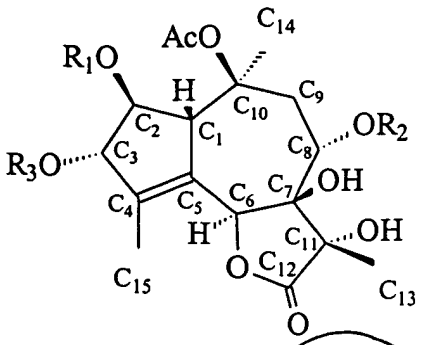
45. The thapsigargin derivative of claim 42, having the following structure



wherein R_1 is a primary amine-containing alkanoyl, alkenoyl, or arenoyl substituent, R_2 is an alkanoyl, alkenoyl, or arenoyl substituent, and R_3 is an alkanoyl or alkenoyl substituent.

46. The thapsigargin derivative of claim 45, wherein R_1 is selected from the group consisting of unsubstituted or alkyl-, aryl-, halo-, alkoxy-, alkenyl-, amido- or amino-substituted CO-$(CH=CH)_{n1}$-$(CH_2)_{n2}$-Ar-NH_2, CO-$(CH_2)_{n2}$-$(CH=CH)_{n1}$-Ar-NH_2, CO-$(CH_2)_{n2}$-$(CH=CH)_{n1}$-CO-NH-Ar-NH_2 and CO-$(CH=CH)_{n1}$-$(CH_2)_{n2}$-CO-NH-Ar-NH_2, wherein n1 and n2 are from 0 to 5, and Ar is any substituted or unsubstituted aryl group.

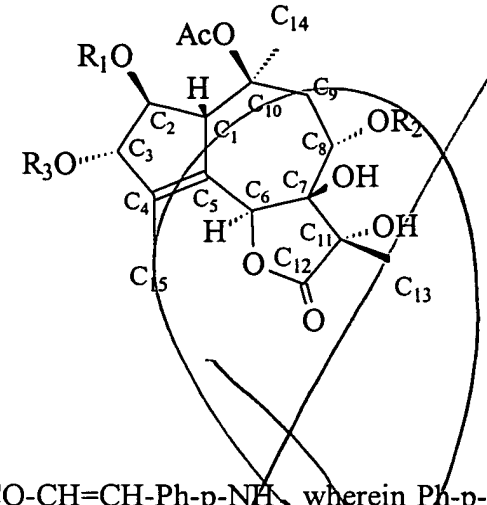
47. The thapsigargin derivative of claim 42, having the following structure



wherein R_1 is an alkanoyl, alkenoyl, or arenoyl substituent, R_2 is a primary amine-containing alkanoyl, alkenoyl, or arenoyl substituent, and R_3 is an alkanoyl or alkenoyl substituent.

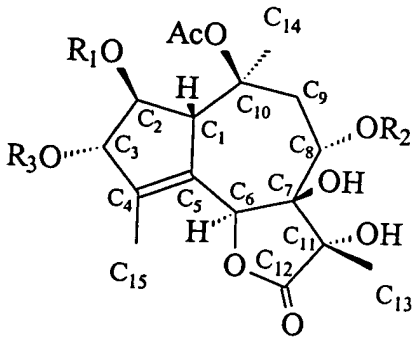
48. The thapsigargin derivative of claim 47, wherein R_2 is selected from the group consisting of unsubstituted or alkyl-, aryl-, halo-, alkoxy-, alkenyl-, amido- or amino-substituted CO-$(CH=CH)_{n1}$-$(CH_2)_{n2}$-Ar-NH_2, CO-$(CH_2)_{n2}$-$(CH=CH)_{n1}$-Ar-NH_2, CO-$(CH_2)_{n2}$-$(CH=CH)_{n1}$-CO-NH-Ar-NH_2 and CO-$(CH=CH)_{n1}$-$(CH_2)_{n2}$-CO-NH-Ar-NH_2, wherein n1 and n2 are from 0 to 5, and Ar is any substituted or unsubstituted aryl group.

49. The thapsigargin derivative of claim 48, having the following structure



wherein R_2 is CO-CH=CH-Ph-p-NH_2 wherein Ph-p-NH_2 is the para-aminophenyl substituent.

50. The thapsigargin derivative of claim 48, having the following structure



wherein R_2 is CO-CH_2-CH_2-Ph-p-NH_2 wherein Ph-p-NH_2 is the para-aminophenyl substituent.

51. The thapsigargin derivative of claim 42, wherein the derivative has an IC_{50} toward ER Ca^{2+}-ATP-ase of at most 500 nM.

52. The thapsigargin derivative of claim 51, wherein the derivative has an IC_{50} toward ER Ca^{2+}-ATP-ase of at most 50 nM.

53. The thapsigargin derivative of claim 42, wherein the derivative has an LC_{50} toward PSA-producing tissue of at most 20 μM.

54. The thapsigargin derivative of claim 53, wherein the derivative has an LC_{50} toward PSA-producing tissue of at most 2.0 μM.

55. A method of producing a prodrug, the method comprising the step of linking
a therapeutically active drug and
a peptide of claim 1,
wherein the linking of the peptide to the drug inhibits the therapeutic activity of the drug.

56. The method of claim 55, wherein the therapeutically active drug has a primary amine.

57. The method of claim 55, wherein the prodrug contains a linker between the peptide and the drug.

58. The method of claim 57, wherein the linker comprises Leu.

59. The method of claim 55, wherein the peptide further comprises a capping group attached to the N-terminus of the peptide, the group inhibiting endopeptidase activity on the peptide.

60. The method of claim 59, wherein the capping group is selected from the group consisting of acetyl, morpholinocarbonyl, benzyloxycarbonyl, glutaryl, and succinyl substituents.

61. A method of treating a PSA-producing cell proliferative disorder, the method comprising administering the composition of claim 19 in a therapeutically effective amount to a subject having the cell proliferative disorder.

62. The method of claim 61, wherein the disorder is benign.

63. The method of claim 61, wherein the disorder is malignant.

64. The method of claim 63, wherein the malignant disorder is prostate cancer.

65. The method of claim 63, wherein the malignant disorder is breast cancer.

66. A method of detecting prostate specific antigen-producing tissue, the method comprising:

contacting the tissue with a composition comprising

a detectably labeled peptide of claim 1 for a period of time sufficient to allow cleavage of the peptide; and

detecting the detectable label.

67. The method of claim 66, wherein the peptide further comprises a capping group attached to the N-terminus of the peptide, the group inhibiting endopeptidase activity.

68. The method of claim 67, wherein the capping group is selected from the group consisting of acetyl, morpholinocarbonyl, benzyloxycarbonyl, glutaryl, and succinyl substituents.

69. The method of claim 66, wherein the detectable label is a fluorescent label.

70. The method of claim 69, wherein the fluorescent label is selected from the group consisting of 7-amino-4-methyl coumarin, 7-amino-4-trifluoromethyl coumarin, rhodamine 110, and 6-aminoquinoline.

71. The method of claim 66, wherein the detectable label is a radioactive label.

72. The method of claim 71, wherein the radioactive label is selected from the group consisting of tritium, carbon-14, and iodine-125.

73. The method of claim 66, wherein the detectable label is a chromophoric label.

74. The method of claim 66, wherein the detectable label is a chemiluminescent label.

75. A method of selecting a prostate specific antigen activatable prodrug wherein the prodrug is substantially specific for target tissue comprising prostate specific antigen-producing cells, the method comprising:

a) linking a peptide of claim 1 to a therapeutic drug to produce a peptide-drug composition;

b) contacting the composition with cells of the target tissue;

c) contacting the composition with cells of a non-target tissue; and

selecting complexes that are substantially toxic towards target tissue cells, but which are not substantially toxic towards non-target tissue cells.

76. A method of determining the activity of prostate specific antigen (PSA) in a sample containing PSA, the method comprising:

a) contacting the sample with a composition comprising a detectably labeled peptide of claim 1 for a period of time sufficient to allow cleavage of the peptide;

b) detecting the detectable label to yield a detection level;

c) comparing the detection level with a detection level obtained from contacting the detectably labeled peptide with a standard PSA sample.

77. A method of imaging PSA-producing tissue, the method comprising:

a) administering a peptide linked to a lipophilic imaging label to a subject having or suspected of having a PSA producing associated cell-proliferative disorder;

b) allowing a sufficient period of time to pass to allow cleavage of the peptide by PSA and to allow clearance of uncleaved peptide from the subject to provide a reliable imaging of the imaging label; and

c) imaging the subject.

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